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Impact of intravesical administration of tranexamic acid on gross hematuria in the emergency department: A before-and-after study

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ABSTRACT

Introduction: Local applications of tranexamic acid (TXA) have been effective in treating various hemorrhagic conditions. In patients with gross hematuria, the main treatment in the emergency department (ED) is continuous bladder irrigation (CBI). However, CBI has no pharmacological effects except blood clot removal from dilution. The aim of this study was to evaluate the impact of the intravesical TXA injection before CBI.
Methods: This study was a before-and-after, retrospective, and single-center study. The target population was hematuria patients who received CBI via a 3-way Foley catheter. As the intervention procedure, 1000 mg of TXA was injected through the Foley catheter and after 15 min, the Foley catheter was declamped and CBI started. Since the intervention started in March 2022, the patients from March 2022 to August 2022 were assigned to the after group and the patients from March 2021 to August 2021 were assigned to the before group. The primary outcomes were the length of stay in the ED and duration of Foley catheter placement. The secondary outcomes were the admissions and the revisits for CBI within 48 h after discharge.
Results: The numbers of patients in the before group and after group were 73 and 86, respectively. The median length of stay in the ED was shorter in the intervention group than in the group not treated with TXA (274 min vs. 411 mins, $P < 0.001$). The median duration of Foley catheter placement was also shorter in the intervention group than not treated with TXA (145 min vs. 308 mins, $P < 0.001$). The revisits after ED discharge were lower in the after group than in the before group (2.3% vs. 12.3%, $P = 0.031$). There was a trend for lower admissions in the TXA treatment group than before group (29.1% vs. 45.2%, $P = 0.052$).
Conclusion: After the TXA intervention, reduction in the length of stay in the ED, the duration of Foley catheter placement, and the revisits after ED discharge was observed.

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1. Introduction

Hematuria is one of the common causes of patients presenting to the emergency department (ED) accounting for approximately 400,000 ED visits annually in the US [1,2]. Causes of hematuria vary from serious underlying diseases such as malignancy to benign diseases such as benign prostatic hyperplasia [3]. Most patients with gross hematuria can be managed on an outpatient basis with instructions encouraging fluid intake, frequent voiding and return precautions for darkening urine, urinary retention, increasing pain, or fever [4]. However, for severe gross hematuria patients at high risk of urinary obstruction by blood clots, continuous bladder irrigation (CBI) through a three-way Foley catheter may be needed to ensure urinary drainage [4]. However, except for reassuring effects on the patient via diluted urine color and prevention of urinary obstruction, CBI itself does not seem to have any pharmacological effect for hemostasis.

Tranexamic acid (TXA) is a synthetic lysine analog that has hemostatic effects by inhibiting plasminogen conversion to plasmin, which hinders fibrinolysis and clot degradation [5]. Due to its various formulation types and relatively mild adverse effects, TXA has been used for various bleeding conditions including epistaxis, trauma, postpartum hemorrhage, traumatic brain injury, and surgical site bleeding [6,7]. Due to concerns about severe complications such as venous thromboembolism in the systemic use of TXA, TXA should be administered topically if the bleeding is localized and topical apply is possible [8,9]. In particular, Moharamzadeh et al. first used topcial bladder administration of TXA to gross hematuria patients and the volume of required saline for CBI to clear urine was significantly reduced [10].

Based on the study, we evaluated the impact of topical TXA administration on the length of stay in the ED and the duration of Foley catheter placement. We hypothesized that patients receiving

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TXA would have reduced length of stay and duration of Foley catheter placement without significant adverse effects.

2. Materials and methods

2.1. Study setting

This was a single-center before-and-after study based upon a retrospective review of electronic medical records (EMRs) in a 1400-bed veterans hospital in Korea with 30,000 annual ED visits. Since November 2015, the study center has implemented a routine protocol for gross hematuria patients that include routine blood tests, urinalysis and CBI with cold saline (4 °C) via a three-way Foley catheter for patients with a gross hematuria grade equal to or >6. For the evaluation of the grade of gross hematuria, an objective grading scale from 1 to 10 was used as shown in a figure in another study [11]. The institutional review board of the study hospital approved the analysis and waived the requirement for informed consent (IRB No 2022–09-009).

2.2. Implementation of topical TXA administration

The implementation of topical TXA administration via Foley catheter was initiated in March 2022. Local TXA administration as the intervention was performed as follows: (1) A three-way Foley catheter was inserted, and residual urine was fully drained. (2) One g of tranexamic acid (Shin Poong Pharmaceutical Company, South Korea) diluted with 100 ml of normal saline was administered via the Foley catheter. (3) After TXA administration, the Foley catheter was clamped to allow the TXA solution to remain in the bladder for 15 min. (4) After 15 min, CBI started with the declamping of the Foley catheter. (5) The Foley catheter was removed when the hematuria grade was lower than 3 and there was no evidence of a blood clot. The Foley catheter was not removed if the patient wished to be discharged with the Foley catheter.

Except for the addition of the TXA administration procedure, the same routine protocol used since 2015 was applied to gross hematuria patients. Fig. 1 shows the schematic flow of the gross hematuria protocol for before and after group. CBI was performed in all patients with a gross hematuria scale of 6 or higher from 2015. In the case of patients with a gross hematuria scale of 5 or less, short-term urology outpatient follow-up was guided without any treatment in ED.

2.3. Study population and data collection

The target study population was patients order than 18 years who visited the ED with gross hematuria. We excluded patients with a hematuria grade less than or equal to 5, patients with initial urinary obstruction in whom initial natural drainage of urine after Foley catheter insertion was impossible, and patients who rejected Foley catheter insertion. We retrospectively reviewed the EMRs of gross hematuria patients injected with TXA solution from March 2022 to September 2022 after the implementation of the intervention (the after group). The EMRs of gross hematuria patients who visited the ED from March 2021 to September 2021 were reviewed as the before group.

Demographic and clinical data were abstracted from the EMRs by 2 independent trained abstractors using standardized data collection forms according to the guideline recommended by Gilbert et al. [12]. As a medical records abstractor, each has 3-year and 4-year experience, respectively. Any discrepancies between the two abstractors were resolved through consensus of authors.

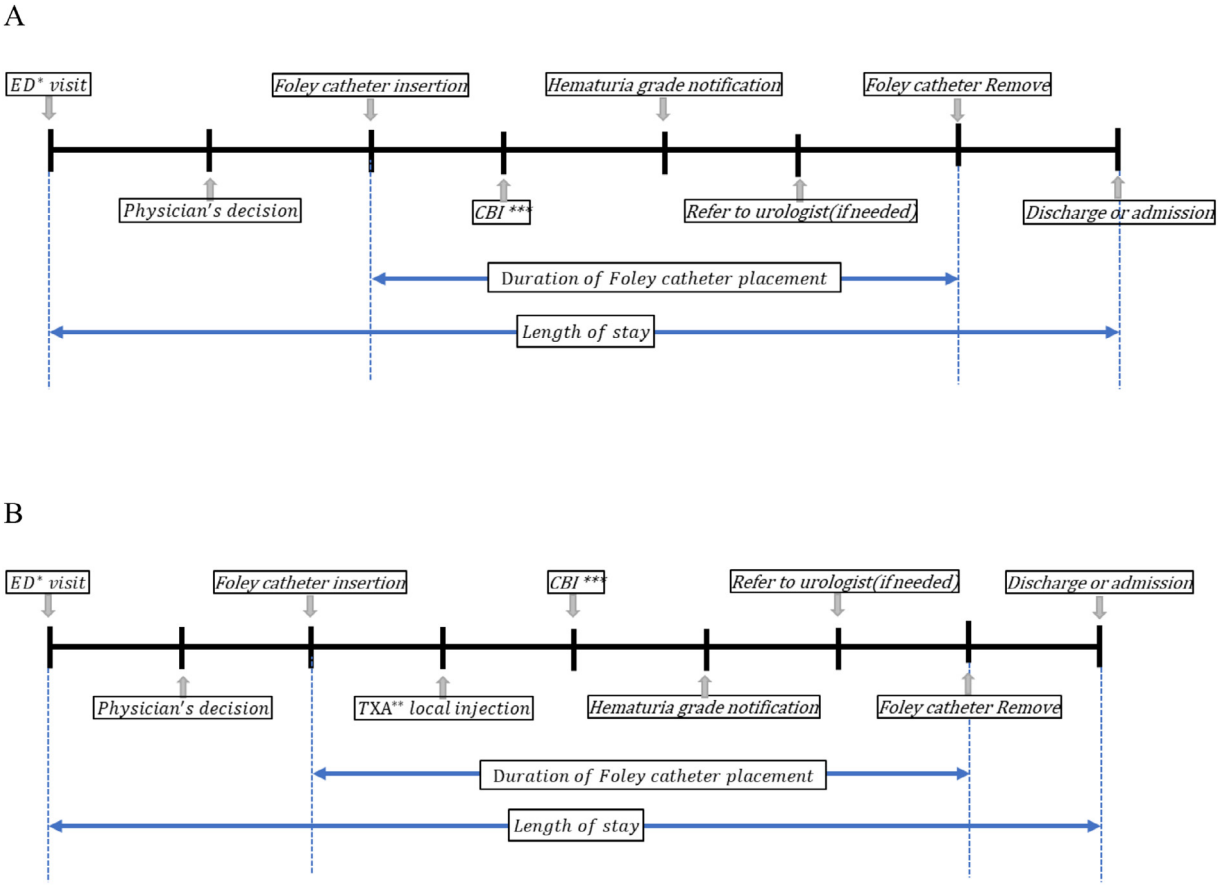

Fig. 1. Schematic flow of gross hematuria protocol.

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2.4. Outcome measures

The primary outcomes were the ED length of stay and the duration of Foley catheter placement. If patients were discharged with a Foley catheter, the discharge time was assumed to be the time that the Foley catheter was removed. The secondary outcomes were the admissions and revisits. A revisit was defined when patients revisited the ED within 48 h of the initial discharge and CBI was performed on the patients again. If there is no significant improvement after treatment through TXA and CBI about for an hour, the patients were admitted to the urology department.

2.5. Statistical analysis

Continuous variables were presented as the means and standard deviations. The continuous variables not normally distributed were represented by median values and interquartile range (IQR). Binomial variables were presented as the frequency of occurrence. Student's *t*-test, Wilcoxon's rank-sum test, the chi-square test, or Fisher's exact test was performed, as appropriate, for comparisons before and after the intervention. All *P* values were 2-tailed, and *P* values <0.05 were considered statistically significant. A piecewise regression discontinuity approach using generalized linear models and interrupted time series analysis were performed to evaluate the impact of the intervention. Additionally, a Box-Pierce test was performed to identify statistically significant autocorrelations in the time series models we used. All data handling and statistical analyses were performed using R-packages, version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics of the study population

Table 1 shows that the two groups appear to have similar baseline characteristics. From the 423 gross hematuria patients who visited the ED during the study period, 159 patients were included in the analysis. Of the 264 excluded patients, 261 had a gross hematuria grade of 5 or less. Therefore, the patients were guided to the short-term outpatient follow up and discharged without any treatment including CBI and TXA injection. Two of the remaining three patients received manual irrigations because there were too many blood clots to do CBI. The other one excluded from the study because the patient was discharged against medical advices. Among the included 159 patients, 73 and 86 patients were assigned to the before and after groups, respectively. The Foley catheter insertion rate of both observation period was not significantly different (34% vs. 41%, $P = 0.135$).

3.2. Outcomes

Median value (IQR) of gross hematuria grade measured at the time of ED visit was 8 (7 to 9) in the before group vs. 8 (7 to 9) in the after group. After irrigation, median value (IQR) of that was 2 (1 to 3) vs. 1(1 to 2).

Table 2 shows the ED length of stay, the duration of Foley catheter placement, the admissions and the revisits. After the implementation of topical TXA administration, the median length of stay was shorter from 411 min to 274 min ($P < 0.001$). Additionally, the median duration of Foley catheter placement was shorter from 308 min to 145 min ($P < 0.001$). The revisits were lower in the after group than in the before group (2.3% vs. 12.3%, $P = 0.024$) (Table 2). There was a trend for lower admissions in the after group compared to the before group (29.1% vs. 45.2%, $P = 0.052$).

Fig. 2 shows monthly trends of the length of stay and the duration of Foley catheter placement by interrupted time series analysis. There was no significant autocorrelation in the time series analysis ($P = 0.132$). In both groups, the monthly trends of the length of stay and the duration of Foley catheter placement showed upward trends, but the trends were not statistically significant difference. Additionally, the slope changes in monthly trends of the length of stay and the duration of Foley catheter placement between the two groups were not statistically significant. However, the immediate effect of the intervention was significant in the length of stay (−302.7 mins, $P < 0.001$) and the duration of Foley catheter placement (−306.9 mins, $P < 0.001$).

Table 1
Baseline characteristics.

	Before group ($N = 73$)	After group ($N = 86$)
Epidemiological data		
Mean age ± SD, years	80.4 ± 6.8	78.4 ± 7.5
Male sex (%)	66(90)	83(97)
Diabetes mellitus (%)	33/73(45)	45/86(52)
Hypertension (%)	57/73(78)	63/86(73)
Cerebrovascular disease (%)	18/73(25)	20/73(23)
Heart disease (%)	20/73(27)	32/73(37)
Liver disease (%)	3/73(4)	5/73(6)
Chronic kidney disease (%)	19/73(26)	21/73(24)
Lung disease (%)	12/73(16)	13/73(15)
Vital signs, mean ± SD		
Systolic blood pressure, mmHg	142 ± 31	143 ± 25
Diastolic blood pressure, mmHg	81 ± 19	82 ± 14
Heart rate, beats/min	87 ± 18	85 ± 16
Respiratory rate, cycles/min	19 ± 2	19 ± 2
Body temperature, °C	36.5 ± 0.3	36.7 ± 0.5
Antithrombotic agents *		
Anticoagulants (%)	12(16)	8(9)
Antiplatelets (%)	27(37)	42(49)
Laboratory findings, mean ± SD		
Blood urea nitrogen, mg/dL	23.0 ± 10.4	24.5 ± 12.6
Creatinine, mg/dL	1.35 ± 0.80	1.44 ± 0.94
Hemoglobin, g/dL	11.9 ± 2.3	11.8 ± 2.2
Platelets, $\times 10^3/\mu L$	219 ± 66	215 ± 73
Prothrombin time, seconds	12.5 ± 1.91	12.3 ± 1.83
International normalized ratio	1.08 ± 0.18	1.08 ± 0.17
Urinalysis		
Urine WBC (%)		
−	45(62)	47(54)
+	9(12)	19(22)
++	11(15)	13(15)
+++	8(11)	7(8)
Urine RBC (%)		
−	0(0)	0(0)
+	0(0)	1(1)
++	2(3)	1(1)
+++	71(97)	84(98)

* The number of patients taking prescribed antithrombotic agents.

4. Discussion

In this study, it was observed that patients given intravesical TXA injection had shorter ED length of stay ($P < 0.001$) and duration of Foley catheter placement ($P < 0.001$). In addition, it was showed that revisits were lower in the TXA treating group ($P = 0.030$). There was a trend for lower admissions in the after group compared to the before group ($P = 0.052$).

In the previous study, it was showed that TXA local injection reduced the amount of normal saline used for CBI, and microscopic hematuria grade after 24 h of TXA treatment [9]. This study has several implications for patients who visit the emergency room with gross hematuria. CBI in gross hematuria patients can increase medical staff burden because it requires constant monitoring of proper urine flow without obstruction and volumes of saline irrigation [13,14]. Therefore, shortening the duration of CBI to reduce the patient length of stay in the ED contribute to preventing ED overcrowding and allowing ED medical staff to concentrate on more serious patients [15]. As the grade of gross hematuria improves and the potential risks of urine flow obstruction are reduced, most patients can be discharged with outpatient follow-up [4].

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Table 2
Primary and secondary outcomes.

	Before group(N = 73)	After group (N = 86)	Difference(95% CI)	*P*-value
Primary outcome, median(minutes)				
Length of stay (IQR)	411(280 to 792)	274(168 to 373)	137(41 to 233)	<0.001
Duration of Foley catheter placement (IQR)	308(201 to 725)	145(81 to 293)	163(67 to 259)	<0.001
Secondary outcome				
Revisits (%)	9(12.3)	2(2.3)	10.0(0.6 to 19.0)*	0.030
Admissions (%)	33(45.2)	25(29.1)	16.1(−0.1 to 32.0)*	0.052

* Proportion difference with 95% confidence interval.

The effectiveness of CBI is mainly due to its dilution effect and prevention of large blood clots [16]. Therefore, if gross hematuria patients are treated only with CBI, additional pharmacological hemostatic effects other than the patient's own physiological hemostasis cannot be expected. Several studies have shown that the hemostatic effect of topical application of TXA is effective for oral bleeding or epistaxis in which topical application is possible by packing [17,18]. Similar effects to TXA packing can be achieved by inserting a Foley

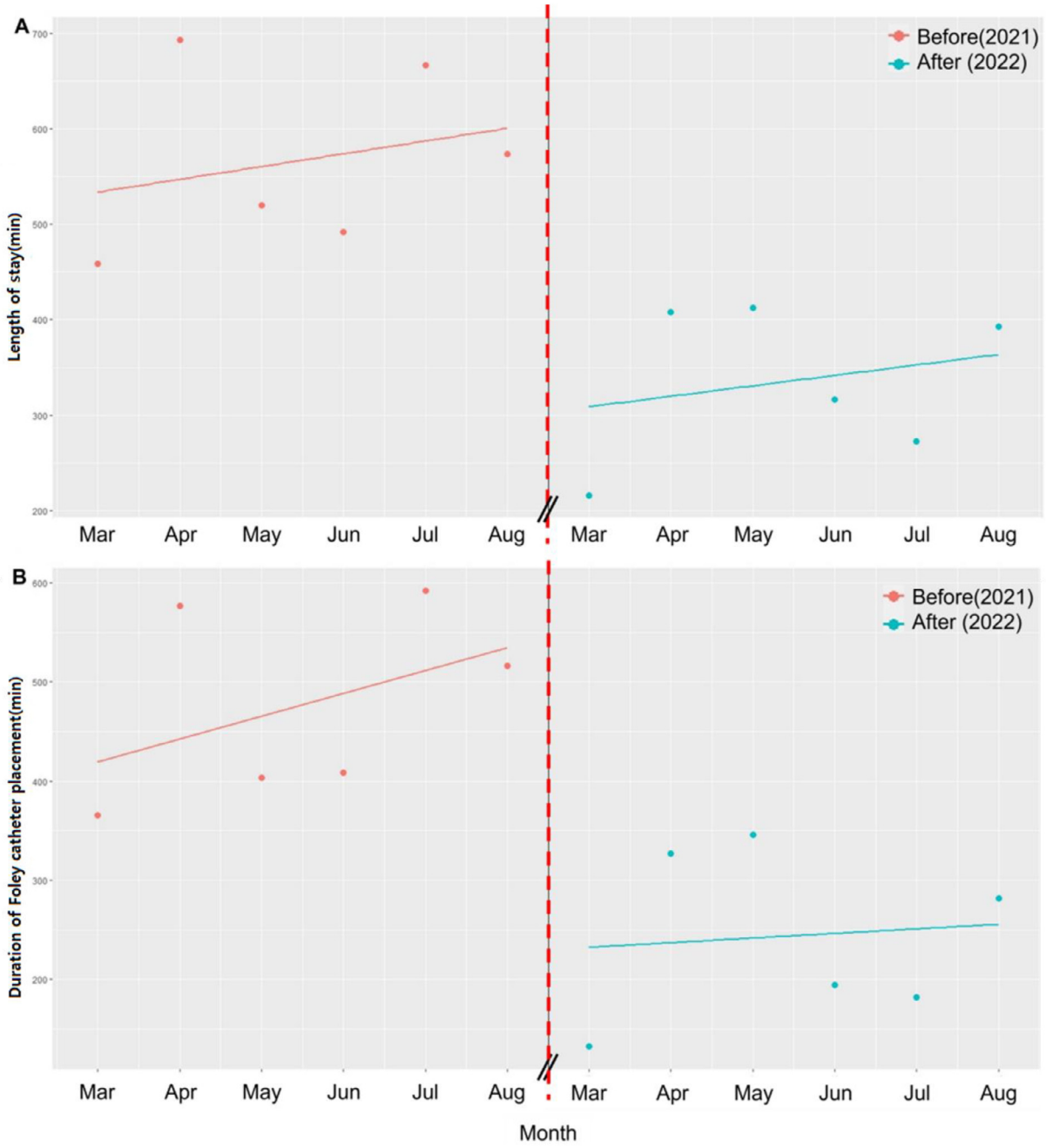

Fig. 2. Monthly trend comparison between the before and after groups.

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catheter, emptying the bladder, administering TXA, and clamping the Foley catheter for 15 min.

Concerns about the side effects of systemic TXA injections, such as venous thrombosis, have persisted [19-21]. If the cause of gross hematuria comes from the upper urinary tract, such as the kidneys or ureter, there is a possibility of exacerbation of AKI due to thrombosis in the renal pelvis or ureter [22]. Therefore, considering the high concentration at bleeding sites and possible systemic side effects of TXA, local administration will be better than systemic injection if topical application is possible. Possible side effects of topical TXA injection are the exacerbation of thrombosis in the bladder and frequent urine output obstruction by blood clots. If such adverse effects were considerable, they would have affected the length of stay in the ED, the duration of Foley catheter placement and revisits.

This study has several limitations. Since, CBI was administered to patients with gross hematuria grade 6 or higher regardless of causes of the hematuria, intravesical TXA may have been administered to patients with gross hematuria from the upper urinary tract rather than the lower urinary tract. However, due to the characteristics of veterans hospitals where mostly elderly men visit, most patients might have gross hematuria from the lower urinary tract, such as bladder cancer or BPH [23].

Second, the method of measuring gross hematuria grade is subjective. There have been many studies that objectively evaluate a grade of gross hematuria, but there are limitations in using the analytical machine such as photoplethysmography in a busy emergency department [13,24]. Additionally, the nurses in charge were not informed that adding the TXA injection step to the existing CBI protocol was to reduce the length of stay and the duration of Foley catheter placement.

Third, there are gap periods of 6 months in observation periods. From November 2021 to February 2022, the study center operated as a hospital dedicated to COVID-19 and the number of patients with gross hematuria was reduced. If these pandemic periods were included in the study periods, there is a possibility of bias caused by confounding factors related to COVID-19 pandemic. In addition, since the proficiency of doctor interns who inserted a Foley catheter showed a monthly trend, the same months among the years was compared. As shown in Fig. 2 the coefficients (slopes) of the linear regression model were not statistically significant in either group and a significant change in slopes by the intervention was not observed. The reason that the statistically significant change was not observed in the interrupted time series analysis could be that adherence to the CBI protocol from 2015 has already reached high level. It might be not difficult for medical staff to adapt to adding the TXA administration step to the long-established CBI protocol.

Finally, there might have been confounding factors than intervention that affected the length of stay of gross hematuria patients. However, the overall length of stay of all patients during the study periods was not significantly different (656 min vs. 640 mins, $P = 0.951$).

In conclusion, the reduction in length of stay of gross hematuria patients was observed after the implementation of the intravesical tranexamic acid injection via a Foley catheter. Further prospective multicenter studies should be performed to evaluate the impact of topical tranexamic acid administration on gross hematuria patients.

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Hyunwoo Choi: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Euigi Jung:** Writing – review & editing, Data curation. **Yu Chan Kye:** Writing – review & editing, Data curation. **Jungyoup Lee:** Writing – review & editing, Data curation. **Sion Jo:** Writing – review & editing, Data curation. **Minwoo Kang:** Writing – review & editing, Data curation. **Dongsung Kim:** Writing – review & editing, Data curation, Conceptualization. **Byunghyun Kim:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

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